PATENT

Attorney Docket No.: 6184.204 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Hjort et al.

Application No.: 09/826,245 Group Art Unit: 1615

Filed: April 4, 2001 Examiner: H. Shiek

Confirmation No: 2682

For: New Pharmaceutical Composition And The Process for its Preparation

DECLARATION UNDER 37 C.F.R. 1.132 OF DR. ASTRID SPILLUM

Mail Stop After Final
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

I, Astrid Spillum, declare as follows:

1. Since November 1991, I have been a Manager within Product Development at Novo Nordisk® A/S. My professional experience formulation and manufacturing of solid dosage forms. A copy of my Curriculum Vitae is attached herewith as Exhibit A. However, I am not a named inventor of the above-identified patent application.

2. I understand that the claims of this application have been rejected as obvious over WO 99/19313 by Lohray.

3. The following experiment was performed under my direction and control. Three different types of formulations of the arginine salt of (-)3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid (hereafter compound A) were prepared to investigate the influence of different formulation principles on the stability of compound A. Wet granulation, melt granulation and direct compression were tested as formulation principles. The strengths of compound A were 0.5 mg and 10 mg in 200 mg tablets. The

tablets were stored in open containers at 40°C/75% RH.

The compositions of the tablets are shown below:

Direct compression:

Compound A	0.354% or 7.08%
Microcrystalline cellulose	20%
Anhydrous lactose	74.6% or 67.9%
Talc	4.5%
Magnesium stearate	0.5%

Process: API and fillers are mixed, talc and magnesium stearate are added separately.

Melt granulation:

Compound A	0.354% or 7.08%
Anhydrous lactose	87.6% or 80.9%
Macrogol 6000	7%
Talc	5%

Process: All ingredients are mixed and heated up to ~ 65°C in a high shear mixer whereby macrogol 6000 melts and granules are formed. Talc is added after cooling.

Wet granulation:

Compound A	0.354% or 7.08%
Microcrystalline cellulose	19%
Lactose monohydrate	79.1% or 72.4%
Talc	1%
Magnesium stearate	0.5%

Process: API and fillers are mixed and granulated with water. Talc and magnesium stearate are added after drying.

The stability of the above formulations were assessed by measuring the amount of impurities by capillary electrophorisis of 0, 1, 3 and 12 months. The data after 6 months were obtained by HPLC analysis.

4. The results from the experiments described in ¶ 3 are given in the table below.

Sum of impurities (capillary electrophoresis, CE) after storage at 40°C/75% RH, open containers.

Formulation	Tablet Strength	Storage time, months				
		0	1	3	6[1]	12
Direct Compression	0.5 mg	0.7%	1.1%	1.0%	0.6%	1.6%
	10 mg	0.3%	0.4%	0.6%	0.9%	1.2%
Melt Granulation	0.5 mg	0.8%	5.6%	5.3%	3.8%	9.3%
	10 mg	0.3%	0.6%	1.5%	1.1%	3.8%
Wet Granulation	0.5 mg	0.6%	4.4%	6.9%	1.8%	5.7%
	10 mg	0.4%	1.6%	2.3%	0.6%	1.9%

1: HPLC impurities (CE not available)

Analysed as above, a low number indicates a better stability of compound A than a high number.

5. The data above therefore clearly show that formulation by direct compression using microcrystalline cellulose, anhydrous lactose, talc and magnesium stearate as excipients is by far superior to either melt granulation using anyhydrous lactose, macrogol and talc as excipients or wet granulation using microcrystalline cellulose, lactose monohydrate, talc and magnesium stearate as excipients. This result was totally unexpected and could not be anticipated by prior to these experiments.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Astrid Spillum

30-Sep-2003
Date

Astrid Spillum

CURRICULUM VITAE

Name:	Astrid Spillum
Date of birth:	18 July 1952
Education:	M.Sc. (Pharm.)
Year:	1976
School/University:	Royal Danish School of Pharmacy

PUBLICATIONS

Acta Pharm. Nord. 3 (3) 131-138 (1991)

International Stability Testing, Brussel 1998
"Meeting Stability Test Requirements when Applying for Global Marketing Authorisation"

Stability Testing, London 1999
"Matrixing: Reducing Stability Testing Costs through Implementing Matrixing"

Date: 15-Sep-2003

Signature: Astrid Spillum

Departments: Product Development, SDF Pilot Plant, Clinical Supplies Operations, Clinical Supplies

CURRICULUM VITAE

Name:	Astrid Spilium
Date of birth:	18 July 1952
Education:	M.Sc. (Pharm.)
Year:	1978
School/University:	Royal Danish School of Pharmacy

EMPLOYMENTS:

Year:	Employed at:	Employed as:	Responsible for:
1971 - 1973	L. Bagger Hansen, Pharmacist	Trainee	
1977	Royal Danish School of Pharmacy	Junior Lecturer	Laboratory lectures in physical chemistry
1977 - 1984	A/S Dumex Pharmaceutical Development	Section Leader Laboratory	Development of pharmaceutical dosage form
1984 - 1991	A/S Dumex Pharmaceutical Development	Manager	All activities within pharmaceutical development laboratory
1991 - 1994	Novo Nordisk A/S Pharmaceutical Development	Manager	All activities within pharmaceutical development Pharmaceuticals Division of solid dosage form
1994	Novo Nordisk A/S Product Development Pharmaceuticals Division	Manager	All activities within pharmaceutical development of new products
1996	Novo Nordisk A/S Product Development Pharmaceuticals Development	Manager	All activities within pharmaceutical development of new products
2000	Novo Nordisk A/S Product Development SDF Pilot Plant Pharmaceuticals Development	Manager	All activities within pharmaceutical development of new products and manufacturing of solid dosage forms for clinical trials
2003	Novo Nordisk A/S Product Development & Clinical Supplies Operations CMC Development	Manager	All activities within pharmaceutical development of new products and manufacturing of solid dosage forms for clinical trials. Distribution and packing of clinical supplies. Local Supplies Coordination and Clinical Supplies Systems.

Date: 15-sep-2003

Signature: [signature]

Department: Product Development, SDF Pilot Plant, Clinical Supplies Operations, Clinical Supplies